

claim 1 was unclear. With regard to claims 3 and 4, the Examiner indicated that these claims were dependent on a cancelled claim.

The Applicants have amended claim 1 to more particularly point out the invention. In particular, the "characteristic of. . ." language referred to by the Examiner has been deleted. Applicants believe the amended claim 1 is clear and definite. Applicants have also amended claim 1 to indicate that the crosslinking agent comprises at least two aldehyde functional groups that are transformed into other functional groups linking the crosslinking agent with the polypeptide growth factor and the substrate. Applicants have also amended claim 3 to depend from claim 1 to correct the claim dependency.

In light of the claim amendments, Applicants respectfully request the withdrawal of the rejections of claims 1, 3, 4 and 8-17 under 35 U.S.C. § 112, second paragraph.

Rejections under Muller-Leirheim

The Examiner rejected claims 1, 11, 15 and 16 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,828,563 to Muller-Leirheim (Muller-Lierheim).

Applicants submit that amended claim 1, and claims 11, 15 and 16 are not anticipated by Muller-Lierheim. The disclosure in Muller-Lierheim relates to covalent bonding of the growth factor to the active groups on the surface of the polymer layer. See Muller-Lierheim, col. 3, lines 40-44. Muller-Lierheim discloses potential active groups on the polymer layer for attaching growth factors.

The present claimed invention includes covalent bonding of the growth factors to the substrate using crosslinking agents comprising at least two aldehyde groups. See Specification, for example, page 17, lines 5-21. The covalent bonding of the growth factor in Muller-Lierheim does not include the use of crosslinking agents with aldehyde functional groups as claimed in the present application.

Since Muller-Lierheim does not disclose the claimed invention, Applicants respectfully request the withdrawal of the rejections of claims 1, 11, 15 and 16 under 35 U.S.C. § 102(b).

Rejections under Guire

The Examiner rejected claims 1, 3, 8, 9, 11, 12, 15 and 16 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,263,992 to Guire (Guire). The Examiner stated that human tissue can be used as the substrate and the growth factors can be used as the bioactive agents in Guire.

Applicants submit that amended claim 1, and claims 3, 8, 9, 11, 12, 15 and 16 are not anticipated by Guire. The present invention uses crosslinking agents with aldehyde functional groups for covalently bonding the growth factor to the substrate. See Specification, page 17, lines, 8-11. The linker molecules of Guire have two different functional groups that are sequentially activated. The photochemical groups in Guire bond at a variety of sites. In contrast, the crosslinking agents claimed in the present invention bond at specific sites on a substrate. There is no disclosure in Guire regarding covalent bonding of growth factors to substrates using crosslinking agents with at least two aldehyde functional groups as claimed in the present invention.

Since Guire does not disclose the claimed invention, Applicants respectfully request the withdrawal of the rejections of claims 1, 3, 8, 9, 11, 12, 15 and 16 under 35 U.S.C. § 102(b).

Rejections under Noishiki

The Examiner rejected claims 1 and 3-4 under 35 U.S.C. § 102(b) as being anticipated by EP 0742020 by Noishiki (Noishiki). The Examiner indicated that attachment of growth factors with glutaraldehyde was known and disclosed in the prior art of Noishiki. The Examiner further stated that the bonding need not be covalent but can be by non-covalent bonding which apparently includes hydrogen bonding, van der Waals interactions, ionic interactions and molecular rearrangements.

Applicants submit that amended claim 1 and claims 3 and 4 are not anticipated by Noishiki. The prior art of Noishiki is related to use of glutaraldehyde to attach a bioabsorbable substance to the prosthesis, not a growth factor to the substrate as in the present application. See Noishiki, col. 4, lines 17-20. Bioabsorbable substances are indicated to be collagen, albumin or gelatin. See Noishiki, for example, col. 1, lines 46-49. The Applicants acknowledge the Examiner's statement that the bioabsorbable substance can be part of the substrate. There is no disclosure, however, in Noishiki regarding attachment of growth factors to the substrate using covalent bonding.

With respect to attaching growth factors, Noishiki states that the "growth factors can be bound directly to the bioabsorbable substance." See Noishiki, column 6, lines 4-5. Noishiki indicates that the growth factors can be bound with various negatively charged substances, i.e. ionic bonding. See

Noishiki, column 10, lines 31-36. There is no disclosure related to the association of the growth factors to the substrate by covalent bonding using crosslinking agents.

Since Noishiki does not disclose the claimed invention, Applicants respectfully request the withdrawal of the rejections of claims 1 and 3-4 under 35 U.S.C. § 102(b).

Rejections under Bayne

The Examiner rejected claims 1, 3-4, 8-9, 12, 13, and 15-16 under 35 U.S.C. § 102(b) as being anticipated by EP 0476983 to Bayne et al. (Bayne). The Examiner indicated that Bayne uses fibrin to associate the growth factor with the substrate.

Applicants submit that amended claim 1 and claims 3-4, 8-9, 12, 13, and 15-16 are not anticipated by Bayne. Bayne discloses the use of fibrin for attachment of vascular endothelial growth factor. Fibrin is a known biological adhesive. The claimed invention does not include the use of fibrin or any other adhesive for attaching the growth factor to the substrate. There is no disclosure in Bayne regarding attachment of vascular endothelial growth factor to a substrate as claimed in the present invention.

Since Bayne does not disclose the claimed invention, Applicants respectfully request the withdrawal of the rejections of claims 1, 3-4, 8-9, 12, 13, and 15-16 under 35 U.S.C. § 102(b).

Rejection over Muller-Lierheim in view of Weatherford

The Examiner rejected claim 13 under 35 U.S.C. 103(a) as being unpatentable over Muller-Lierheim in view of Weatherford. The Examiner indicated that Muller-Lierheim

discloses attaching growth factors to implants but fails to teach attaching vascular endothelial growth factor (VEGF) to a substrate. The Examiner also indicated that Weatherford teaches that it was known to attach VEGF to similar implants. The Examiner indicated that it would have been obvious to one of ordinary skill in the art to attach VEGF to a Muller-Lierheim implant in order to promote vascular endothelial cell growth thereon.

Applicants submit that there is no teaching or suggestion in Muller-Lierheim when combined with Weatherford that results in the invention as claimed in claim 13, dependent on amended claim 1. There is no teaching or suggestion in either cited reference, alone or combined, related to covalent bonding using crosslinking agents comprising at least two aldehyde functional groups. As discussed above, Muller-Lierheim is related to bonding with active groups on the polymer surface. The discussion in Weatherford relates to the use of fibrin glue with VEGF and heparin. Weatherford is silent with respect to covalent bonding of VEGF to a substrate and its effectiveness for stimulating association of viable cells.

Since the combination of Muller-Lierheim and Weatherford does not teach or suggest covalent bonding of growth factors to substrates using crosslinking agents having at least two aldehyde functional groups, Applicants respectfully request the withdrawal of the rejection of claim 13 under 35 U.S.C. § 103(a) as being unpatentable over Muller-Lierheim in view of Weatherford.

Rejection over Guire in view of Goldstein

The Examiner rejected claim 10 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,263,992 to Guire (Guire) in view of U.S. Patent No. 5,613,982 to Goldstein (Goldstein). The Examiner indicated that Guire discloses the use of human tissue as the implant substrate material but fails to disclose the use of animal tissue therefor. The Examiner also indicated that Goldstein teaches that it was known to use porcine tissue for similar implants. The Examiner concluded that it would have been obvious to use porcine tissue as the tissue substrate of Guire.

Applicants submit that there is no teaching or suggestion in Guire when combined with Goldstein that results in the invention as claimed in claim 10, dependent on amended claim 1. There is no teaching or suggestion in either cited reference related to covalent bonding using crosslinking agents wherein the crosslinking agents have at least two aldehyde functional groups. As discussed above, the discussion in Guire is related to bonding using linker molecules that are activated sequentially. See Guire, Col. 4, lines 58-61. The discussion in Goldstein relates to the use of porcine tissue. Goldstein does not teach or suggest attaching growth factors to substrates using crosslinking agents as in the present claimed invention.

Since the combination of Guire and Goldstein does not teach or suggest covalent bonding of growth factors to substrates using crosslinking agents with at least two aldehyde functional groups as claimed in this application, Applicants respectfully request the withdrawal of the rejection of claim 13 under 35 U.S.C. § 103(a) as being unpatentable over Guire in view of Goldstein.

Rejection over Bayne

The Examiner rejected claim 17 under 35 U.S.C. 103(a) as being unpatentable over EP 0476983 to Bayne (Bayne). The Examiner indicated that Bayne meets the claim language except for the sterilizing and packaging of the implant as claimed. The Examiner indicated that sterilizing and packaging of medical materials for distribution has been known in the art.

Applicants submit that Bayne does not teach or suggest claim 17, dependent on amended claim 1. As discussed above, Bayne discusses the use of fibrin. Applicants submit that there is no teaching or suggestion in Bayne related to attaching growth factors to a substrate as claimed in the present invention.

Applicants submit that claim 17, dependent on amended claim 1, is not obvious. Applicants respectfully request the withdrawal of the rejection of claim 17 under 35 U.S.C. § 103(a) as being unpatentable over Bayne.

Claim objection

The Examiner objected to claim 14 as being dependent on a rejected base claim. Applicants submit that amended claim 1 is now allowable. Thus, Applicants respectfully request the withdrawal of the objection to claim 14.


CONCLUSIONS

Applicants submit that this application is in condition for allowance, and such action is respectfully requested. The Examiner is invited to telephone the undersigned agent to discuss any questions or comments that the Examiner may have.

The Commissioner is authorized to charge any fee deficiency required by this paper or credit any overpayment to Deposit Account No. 23-1123.

Respectfully submitted,

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